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REVIEW

1,3,4-Oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives as potential antibacterial agents

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1,3,4-Thiadiazole;
1,2,4-Triazole;
Antibacterial agents

Abstract Since the introduction of the first antibiotic (penicillin, 1942) into medical practice, to date, there has been an ongoing "race" between scientists creating new drugs and pathogenic bacteria. Antibiotic-bacteria are becoming progressively common, and to make matters worse, more and more bacteria are becoming resistant to all known antibiotics. The traditional method for this problem is to introduce new antibiotics that kill the resistant mutants. This specific "arms race" resulted into thousands of potentially active chemicals are synthesized in laboratories around the world every day.

1,3,4-Oxadiazole; 1,3,4-thiadiazole; 1,2,4-triazole and some of their derivatives are involved in modifications at the following axes: *First*, attaching a thio-group into heterocyclic rings. *Second*, introducing different substitutions at position 5 which often are the residuals of the synthetic starting materials such as simple aliphatic, substituted aliphatic chains, aromatic carbocyclic and heterocyclic residues.

Contents

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0. Introduction

Deciding whether any bacterium should be considered *susceptible* or *resistant* to any antimicrobial involves an integrated assessment of *in vitro* activity, pharmacologic characteristics, and clinical evaluation. Any agent approved for clinical use has demonstrated *in vitro* its potential to inhibit the growth of some target group of bacteria at concentrations that can be achieved with acceptable risks of toxicity. That is, the minimum inhibitory concentration (MIC) can be comfortably exceeded by doses tolerated by the patient. Use of the antimicrobial in animal models and then human infections must have also demonstrated a therapeutic response. Because the influence of antimicrobials on the natural history of different cate-

gories of infection (e.g., pneumonia, meningitis, and diarrhea) varies, extensive clinical trials must include both a range of bacterial species and infected sites (e.g., lung, bone, CSF). The clinical studies are important to determine whether what *should* work actually *does* work and, if so, to define the parameters of success and failure. MICs must be below achievable blood level. Clinical experience must validate *in vitro* data.

Once these factors are established, the routine selection of therapy can be based on known or expected characteristics of organisms and pharmacologic features of antimicrobial agents. With regard to organisms, use of the term susceptible (sensitive) implies that their MIC is at a concentration attainable in the blood or other appropriate body fluids (e.g., urine) using the usually recommended doses. Resistant, the converse of susceptible implies that the MIC is not exceeded by normally attainable levels. As in all biological systems, the MIC of some organisms lies in between the susceptible and resistant levels. Borderline strains are called intermediate, moderately sensitive, or moderately resistant, depending on the exact values and conventions of the reporting system. The antimicrobial in question may still be used to treat these organisms but at increased doses. For example, nontoxic antibiotics such as the penicillins and cephalosporins can be administered in massive doses and may thereby inhibit some pathogens that would normally be considered resistant *in vitro*. Furthermore, in urinary infections, urine levels of some antimicrobial agents may be very high, and organisms that are seemingly resistant *in vitro* may be eliminated (Cole et al., 2011).

For example sulfonamides and azoles, sulfonamides are structural analogs of *para*-aminobenzoic acid (PABA) and compete with it for the enzyme (dihydropteroate synthetase), which combines PABA and pteridine in the initial stage of folate synthesis. This blockage has multiple effects on the bacterial cells; the most important of these is disruption of nucleic acid synthesis. The effect is bacteriostatic, and the addition of PABA to a medium that contains sulfonamide neutralizes the inhibitory effect and allows growth to resume. When introduced in the 1940s, sulfonamides had a very broad spectrum (*staphylococci*, *streptococci* and many Gram-negative bacteria), but resistance developed quickly, and this has restricted their use for systemic infections. Now their primary use is for uncomplicated urinary tract infections caused by members of the Enterobacteriaceae family, particularly *Escherichia coli*. Sulfonamides are convenient for this purpose because they are inexpensive, well absorbed by the oral route, and excreted in high levels in the urine (Shegam, 2006; Wheelis, 2007; Dimova and Perisic-Janjic, 2009; Lindsay et al., 1994). Five membered ring sulfonamides are closely related to azasolone and similar related structures such as 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazoles.

A survey of literature reveals that 1,4-disubstituted thiosemicarbazides as well as 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazoles and their amino derivatives are known as promising antimicrobial agents (Dimova and Perisic-Janjic, 2009; Lindsay et al., 1994; Salgin-Goksen et al., 2007; Tehranchian et al., 2005; Turan-Zitouni et al., 2005; Ahoya et al., 2011; Belkadi and Othman, 2006, 2011; Khiati et al., 2007; Benhammadi et al., 2010). Compounds of the said structure often exhibit higher activity than standard antibiotics, penicillin G (Salgin-Goksen et al., 2007), ampicillin and gentamicin (Shafiee et al., 2002). On the other hand, various reports reveal that the introduction of halogen atoms into the pharmacophore structure can be beneficial for antimicrobial activity so far as this improves the lipid-solubility of the active ingredients (Kitani et al., 1997; Tang et al., 1998).

In spite of a large number of antibiotics and chemotherapeutics available for medical use, the antimicrobial resistance created a substantial need for a new class of antimicrobial agents in the last decades (Clinical and Laboratory Standards Institute, 2006). Hydrazide hydrazones (are synthetic intermediates in the synthesis of 1,3,4-oxadiazole, 1,3,4-thiadiazole, and 1,2,4-triazoles) form a class of compounds possessing a wide range of biological activities viz. antimicrobial (Baluja et al., 2007) and antimycobacterial (Foroumadi et al., 2006).

Non-steroidal antimicrobial drugs (NSAMDs) represent a heterogeneous family of pharmacologically active compounds. A literature survey revealed that substances liked to 1,3,4-oxadiazole (Bhatia and Gupta, 2011), 1,3,4-thiadiazole (Badran et al., 2007) and 1,2,4-triazole (Plech et al., 2011) moieties have occupied a unique position in the design and synthesis of biologically active agents with remarkable antibacterial, analgesic and anti-inflammatory activities.

1. 1,3,4-oxadiazole and its derivatives

1.1. Introduction

The urgent need for new antibiotics is mainly due to the increase in the frequency of bacterial infections with resistant strains, especially Gram-positive organisms, in both the hospital and community settings. Oxazolidinones are a relatively new class of antibiotics that inhibit bacterial protein synthesis by preventing binding of the aminoacyl-tRNA to the A site of the ribosome (Locke et al., 2010).

1,3,4-Oxadiazole (**1**) is a thermally stable neutral aromatic molecule. Out of its four possible isomers **1**–**4**, 1,3,4-oxadiazole (**1**) is widely exploited for various applications (Nagaraj et al., 2011). Other aromatic related systems are 1,3,4-oxadiazolines (**2**), 1,3,4-oxadiazolium cations (**3**), and the exocyclic-conjugated mesoionic 1,3,4-oxadiazole (**4**) (Nagaraj et al., 2011) (Fig. 1).

X-Linked substituents to aromatic moieties normally appearing at positions C2, C5 and N4 may be represented by following structural features **5**–**8** (Hill, 1984) (Fig. 2).

Also known are derivatives of the non-aromatic reduced systems, 2,3-dihydro-1,3,4-oxadiazole (**9**), 2,5-dihydro-1,3,4-oxadiazole (**10**), and 2,3,4,5-tetrahydro-1,3,4-oxadiazole (**11**) (Hill, 1984) (Fig. 3).

The electronic distribution in 1,3,4-oxadiazole has been calculated by versious SCF-MO methods (Kakitani and Kakitani, 1977). Other structural parameters, dipole moment and data to its Ultraviolet-visible (γ_{max} calculated to be in the region 193–203 nm), NMR, NQR and microwave spectra have been derived. Studies on 1,3,4-oxadiazole indicate a

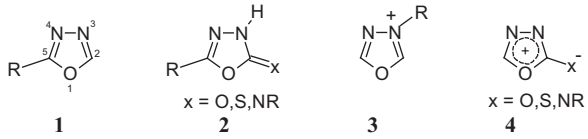


Figure 1 Some aromatic systems of 1,3,4-oxadiazole.

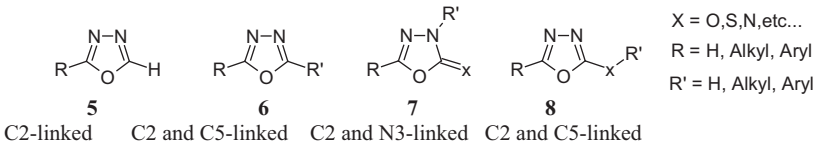


Figure 2 Different positions of substitution in 1,3,4-oxadiazoles.

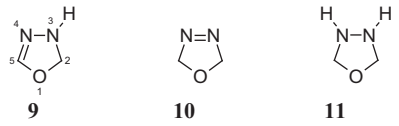


Figure 3 Some non-aromatic systems of hydro-1,3,4-oxadiazoles.

maximum positive charge in the 2-position (Ha, 1979). Molecular diagrams for 1,3,4-oxadiazole, 2-phenyl- and 2,5-diphenyl-1,3,4-oxadiazole, and oligomeric oxadiazoles have been derived and conjugation between the rings is found to be similar to that in polyphenyls (Kosobutskii et al., 1972). Calculated ionization potentials for 1,3,4-oxadiazole (**1**) and 1,3,4-oxadiazoline-5-one (**2**, X═O) have been compared with values from PE spectra (Paine and Werstiuk, 1978).

1.2. Synthesis of 1,3,4-oxadiazole and derivatives

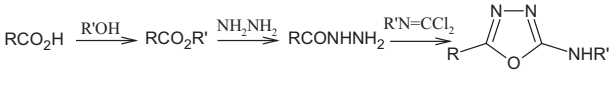
Various methods were reported in the literature for the synthesis of 1,3,4-oxadiazole and its derivatives (Wang et al., 2007). The most widely applicable route to the synthesis of 1,3,4-oxadiazole and its 2,5-disubstituted derivatives is the thermal, acid and base catalyzed cyclization of their corresponding carbonylhydrazides (Hill, 1984). The hydrazide prepared from carboxylic acid *via* an ester can be regarded as the real starting material for the synthesis of 1,3,4-oxadiazole *by* treating the latter with isocyanide dichlorides (Ollis and Ramsden, 1971) (see Scheme 1).

Several carbonylhydrazide derivatives have been synthesized in our laboratory starting from the appropriate carboxylic acids. The common method is described by converting the carboxylic acid to corresponding ester which on treatment with hydrazine gives the corresponding hydrazides. The hydrazide derivatives (1,2-diacylhydrazines and related compounds) are thermally on acid catalysis give 1,3,4-oxadiazole (Hill, 1984) as shown in Scheme 2.

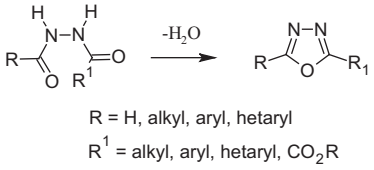
In another way when hydrazides were treated with CS_2 in basic medium it resulted in 2-R-5-mercaptyl derivatives as illustrated in Scheme 3 (Ollis and Ramsden, 1971; Gaetano et al., 1991).

1.3. Tautomerism in 1,3,4-oxadiazole

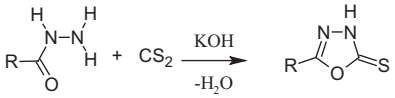
2-Hydroxy (**12a**), 2-mercapto (**12b**) and 2-amino-oxadiazoles (**12c**) are in equilibrium with the tautomeric oxadiazolines



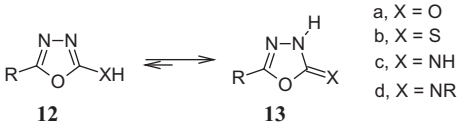
Scheme 1 General synthetic method for 1,3,4-oxadiazole.



Scheme 2 General synthetic method for 1,3,4-oxadiazole.



Scheme 3 General synthetic method for 1,3,4-oxadiazole-5-thiones.



Scheme 4 Tautomerism of thiol thione forms.

(**13a**), (**13b**) and (**13c**) respectively (Aydogan et al., 2002; Giudicelli et al., 1969) (Scheme 4).

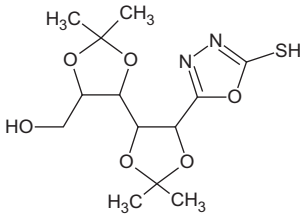
Evidence from U.V, IR, H1-NMR and C13-NMR spectra supports structure **13b** for 1,3,4-oxadiazoline-5-thione. The U.V and IR spectra, fluorescence and pK values of 2-amino-1,3,4-oxadiazoles indicate that the amine tautomer (**12c** or **12d**) rather than the imine tautomer (**13c** or **13d**) predominates (Khiati et al., 2007).

1.4. Antibacterial activity

A variety of Mannich bases derived from 1,3,4-oxadiazole-5-thiones show fungicidal activity and in some cases also act as bactericides and insecticides. Various derivatives for 1,3,4-oxadiazole-5-thiones with R substituents distributed over positions C2,N4 and C5 were synthesized and assigned for antibacterial activity (Ollis and Ramsden, 1971; Kumar et al., 2011).

1.4.1. From gluconic acid

The C-nucleoside possessing 1,3,4-oxadiazolo-2-thiol (**14**) ring derived from gluconic acid was found to have appreciable effects in antibacterial activity against: *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa* and *E. coli* using ampicillin as standard.



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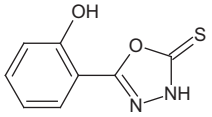
The oxadiazole residues were found to exhibit higher inhibition effects against these bacteria (Belkadi and Othman, 2011).

1.4.2. From salicylic acid

5-(2-Hydroxyphenyl)-1,3,4-oxadiazole-2-thione (**15**) has been synthesized from salicylic acid. Antibacterial activity was investigated *in vitro* against *E. coli* and *S. aureus* using ampicillin and gentamycin as references.

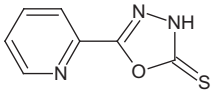


15

The screening results indicate that the compound showed a moderate to slight activity against other tested bacteria (Khiati et al., 2007).

1.4.3. From pyridine carboxylic acids

5-(2-Pyridyl)-1,3,4-oxadiazole-2-thione (**16**) has been synthesized from the corresponding 2-pyridine carboxylic acid (picolinic acid) and tested *in vitro* against the following microorganisms: *E. coli*, *P. aeruginosa*, *Enterococcus faecalis*, *S. aureus*, *P. aeruginosa* and compared with the known antibiotics cephalosporin and gentamycin.

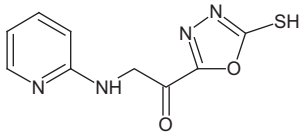


16

Oxadiazole derivative **16** has relatively lower inhibition effect on *S. aureus* and *E. coli* but exhibited more effect on *P. aeruginosa* (Belkadi and Othman, 2006).

1.4.4. From pyridin-2-amine

1-(5-Mercapto-1,3,4-oxadiazol-2-yl)-2-(pyridine-2-ylamino)ethanone (**17**) has been synthesized from 2-(pyridine-2-ylamino) acetohydrazide. This compound was found to have significant antimicrobial activity. The findings of the study indicate that cyclization of the hydrazide acid group of 2-(pyridine-2-ylamino) acetohydrazide into 1,3,4-oxadiazole nucleus resulted in increased antimicrobial activity.

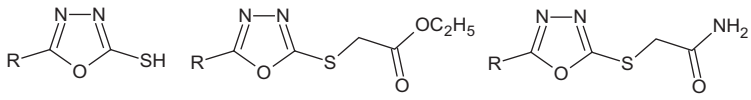


17

The antibacterial activities of the compound **17** were tested against some pathogenic microorganisms: *S. aureus*, *Streptococcus viridians* and *E. coli* and found to have good antimicrobial activity with higher value of MIC. From structure-activity relationships, introduction of the 1,3,4-oxadiazole ring into compound significantly increases their biological activity. The oxadiazole ring system could be incorporated into many more ring systems which have their own activity and could lead to more potent and highly active compounds (Salimon et al., 2011).

1.4.5. From acylhydrazine-S-derivatives

Some novel derivatives of acylhydrazine such as; 5-substituted-2-mercapto-1,3,4-oxadiazoles **18**(**a**–**g**), their corresponding S-esters **19**(**a**–**g**) and amides **20**(**a**–**g**), have been synthesized.



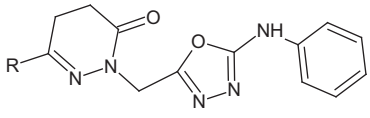
18 **19** **20**

R = (a) -C $_6$H$_5$; (b) -C $_6$H$_4$CH$_3$(3) ; (c) -C $_6$H$_4$OCH $_3$(3) ; (d) -C $_6$H$_4$Cl(2) ; (e) -C $_6$H$_4$Cl(3) ; (f) -C $_6$H$_4$Cl(4) ; (g) -C $_5$H$_4$N(3)

Those compounds have been tested *in vitro* for their antibacterial activity against *E. coli* bacteria by the agar well diffusion method using roxithromycin and cefixime as standard drugs. The results showed that all compounds were active against *E. coli* except **20f** (Zareef et al., 2008).

1.4.6. From β-aroyl propionic acids

A series of 5-{3-oxo-6-(substituted aryl)-2,3,4,5-tetrahydropyridazin-2-ylmethyl}-2-substituted 1,3,4-oxadiazole (**21**) have been synthesized from β-aroyl propionic acids.



21(a-e)

R = (a) H ; (b) 3,5-(CH $_3$)$_2$-C$_6$H$_5$; (c) 4-CH $_3$-C$_6$H$_5$;
(d) 4-(OC $_6$H$_5$)-C$_6$H$_5$; (e) 4-Cl-C $_6$H$_5$

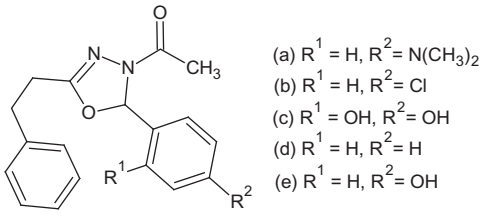
All the compounds are evaluated for their antibacterial activity against *E. coli*, *S. aureus*, *Micrococcus luteus* and *Klebsiella pneumoniae* by using the cup plate technique in the nutrient agar. Antitubercular activity was determined using the BACTEC 460 system. All the synthesized compounds were screened against *Mycobacterium tuberculosis* H37 Rv comparable with that of standard rifampicin and isoniazid. From the results, it was

observed that most of the compounds were active against the microorganism having significant activity against these bacteria comparable to standard drugs, ampicillin and chloramphenicol.

The above synthesized compounds showed the percentage inhibition ranging from 48 to 91%. Compound **21a** was a highly active analog in this series with 91% inhibition against *M. tuberculosis* H37 Rv comparable with that of standard rifampicin and isoniazid (Islam et al., 2008).

1.4.7. From phenylpropionohydrazides

The newly synthesized compounds **22(a–e)** from phenyl propionohydrazides were screened for antibacterial activity against freshly cultured strains of *S. aureus* and *P. aeruginosa* using ampicillin as standard.



22

Among newly synthesized derivatives, compounds **22(a–b)** were found to be equipotent to ampicillin when tested against the strains of *S. aureus*, and *P. aeruginosa*, whereas some of the newly synthesized compounds like **22a**, **22d** and **22e** were found to possess good antibacterial activity when tested against *S. aureus* and *P. aeruginosa*.

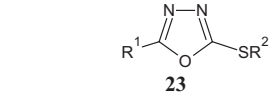
After comparing the antimicrobial results of compounds **22(a–e)**, it was concluded that the incorporation of an oxadiazole moiety in phenylpropionyl derivatives enhances their antimicrobial activity and also para-substitution in the R^2 group of the oxadiazoles was found to enhance their potency, especially in compounds **22(a–b)** (Fuloria et al., 2009).

1.4.8. Alkyl, alkenyl, sulfonyl, thiocarbamates and Mannich derivatives

Alkyl, alkenyl, sulfonyl, thiocarbamates and Mannich derivatives **23–26** were synthesized.

All tested compounds were assayed for their antimicrobial activity against three standard bacterial strains, *S. aureus*, *E. coli* and *P. aeruginosa*.

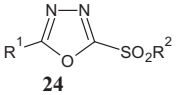
The lowest concentration which inhibited growth was considered as the MIC.



23

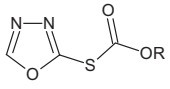
(a) R1 = 4-pyridyl ; R2 = -CH=C-CH2

(b) R1 = Phenyl ; R2 = -CH=C=CH2



24

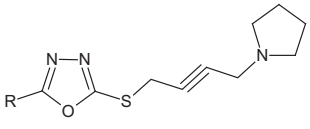
R1 = Phenyl ; R2 = isopropyl



25

(a) R = Benzyl

(b) R = Et



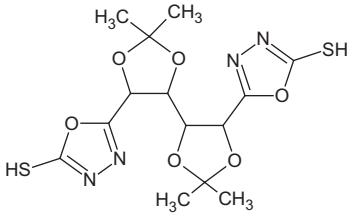
26

R = Phenyl, 4-pyridyl

The MIC for the synthesized compounds indicates that the conversion of the sulfhydryl group in 1,3,4-oxadiazole into alkyl **23a**, allene **23b**, sulfonyl **24** derivatives and mannich product **26** showed a weak antimicrobial activity. However, thiocarbamates **25a** and **25b** were effective against Gram positive and Gram negative bacteria (Muhi-eldeen et al., 2008).

1.4.9. From glucaric acid

This bis(1,3,4-oxadiazole-2-thiol) (**27**) derivative of glucaric acid was essayed for antibacterial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* using ampicillin as reference drug.

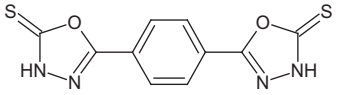


27

The oxadiazole exhibited higher inhibition effects against these bacteria as compared with drug reference (Belkadi and Othman, 2011).

1.4.10. From terephthalic acid

5,5′-benzene-1,4-diylbis(1,3,4-oxadiazole-2-thione) (**28**) was synthesized from terephthalic acid and tested *in vitro* against *E. faecalis* and *E. coli* and compared with known antibiotics cephalosporin and gentamycin.



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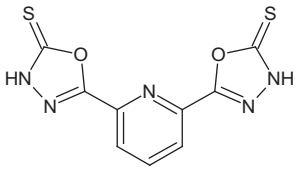
The compound showed an intermediate effect on *E. faecalis* and *E. coli* (Datoussaid et al., 2012).

1.4.11. From pyridine carboxylic acids

The bis-5-(2,6-pyridyl)-1,3,4-oxadiazole-2-thione (**29**) has been synthesized from 2,5-pyridine dicarboxylic acid, and tested *in vitro* against the following microorganisms: *E. coli*, *P. aeruginosa*, *E. faecalis*, *S. aureus* and *P. aeruginosa* and compared with the known antibiotics cephalosporin and gentamycin.



29

The results have shown that the synthesized compound **29** has very high effect in comparison to pyridine mono oxadiazole ring **16** on the gram-negative bacteria *P. aeruginosa* in particular, where its effect exceeded that of the well-known cephalosporin (Benhammadi et al., 2010).

Table 1 Effect of investigated compounds of types of bacteria.

Compounds	Gram positive bacteria	Gram negative bacteria
14	+	+
15	+/–	+/–
16	+/–	+
17	+	+
18	/	+
19	/	+
20	/	+
21	+	+
22	+	+
23	+/–	+/–
24	+/–	+/–
25	+	+
26	+/–	+/–
27	+	+
28	+/–	+/–
29	–	+

+ Positive effect.
– Negative effect.
+/– Moderate effect.

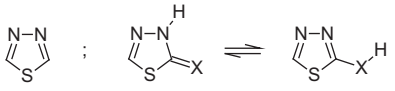
1.4.12. Conclusions

1,3,4-oxadiazoles and their thione derivatives proved to be effective against different microorganisms as summarized in Table 1.

2. 1,3,4-Thiadiazole and its derivatives

2.1. Introduction

1,3,4-Thiadiazoles (**30**) and (**31**) were first described in 1882 by Fischer and further developed by Busch. Thiadiazoles carrying mercapto, hydroxyl and amino substituents can exist in many tautomeric forms and this property is being intensively studied (Kornis, 1984).

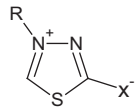


30 **31a** **31b**

1,3,4-Thiadiazoles are conveniently divided into three subclasses:

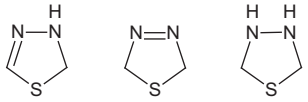
(a) Aromatic systems which include the neutral thiadiazoles **30**.

(b) Mesoionic systems **32** which are defined as five-membered heterocycles which are non-covalent or polar and possess a sextet of electrons in association with the five atoms comprising the ring.



32

(c) Non-aromatic systems such as 1,3,4-thiadiazolines (**33**) and (**34**) and the tetrahydro-1,3,4-thiadiazolidines (**35**).



33 **34** **35**

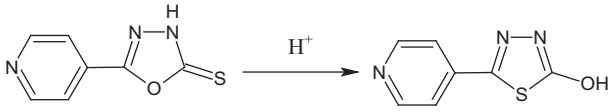
2.2. Synthesis of thiadiazoles and their derivatives

The syntheses of thiadiazoles are discussed in terms of the number of bonds being formed and by ring transformation. Thiadiazole synthesis by one-bond formation is exemplified by cyclization of an acylated thiosemicarbazide as shown in Scheme 5 (Treppendahl and Jackobsen, 1977):

The synthesis of other simple mercapto-thiadiazoles is outlined in Scheme 6: (El-Sayed and Wasfy, 2005):

The most common two bond formation takes place *via* 1,3-dipolar cycloaddition presented in Scheme 7 (Dickore and Wegler, 1966):

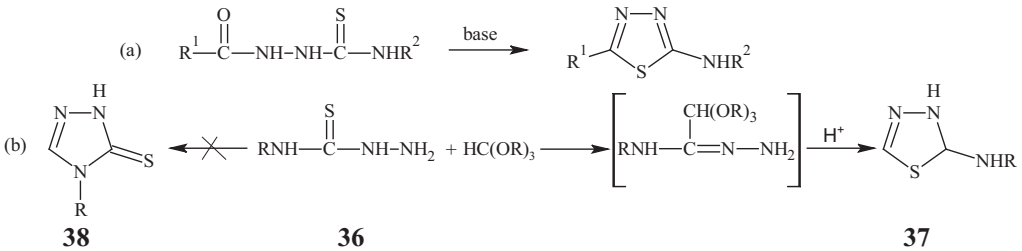
1,3,4-Thiadiazoles can easily be obtained from 1,3,4-oxadiazoles thus in refluxing **43** in ethanolic HCl rearranges to **44** (Giammanco, 1965).



43 **44**

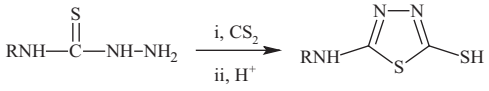
2.3. Tautomerism

The 1,3,4-thiadiazole ring system, with three heteroatoms, does not exhibit tautomerism in its fully conjugated form 30. However, when certain substituents are present, tautomerism is possible. 1,3,4-Thiadiazolin-2-ones (**45a**, **X=O**) and -2-thi-



38 **36** **37**

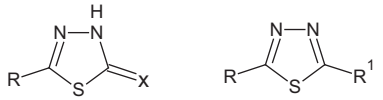
Scheme 5 Synthesis of thiadiazoles.



36 **39**

Scheme 6 Synthesis of mercapto-thiadiazoles.

one (**45b**, **X**=**S**) exist in the oxo and thione forms, respectively, as shown by spectroscopic and LCAO-MO calculations.



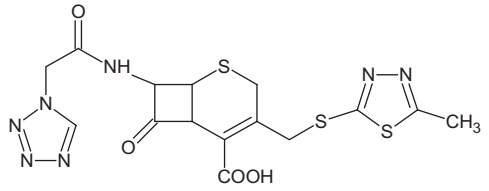
45a, X=O
45b, X=S

46

2-Amino-1,3,4-thiadiazoles exist in the amino form **46** (R^1=NH_2) in solution and in the solid state (Elguero et al., 1976).

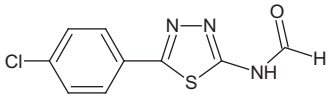
2.4. Antibacterial activity

1,3,4-Thiadiazoles have activity on many biological systems. Cefazolin (**47**) is a thiadiazole analog of cephalosporanic acid useful as antibacterial (Chabbert and Lutz, 1978).



47

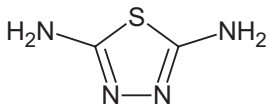
Another compound (**48**) is a patent as bactericidal (Omprakash et al., 2011).



48

2.4.1. From semicarbazide hydrochloride

A bioactive ligand, 2,5-diamino-1,3,4-thiadiazole (**49**), derived from semicarbazide hydrochloride, and its metal complexes were prepared and characterized (Obaleye et al., 2011).

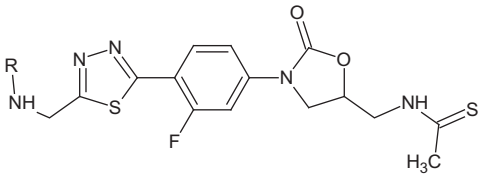


49

In vivo evaluation of the antimicrobial activities of the metal complexes and the ligands showed greater activity against some micro-organisms when compared to the parent compounds (Obaleye et al., 2011).

2.4.2. Thiadiazole phenyl oxazolidinone analogs

Replacement of the morpholine C-ring of Linezolid with a 1,3,4-thiadiazolyl ring leads to oxazolidinone analogs **50**(**a**–**d**) having potent antibacterial activity against both gram-positive and gram-negative organisms.



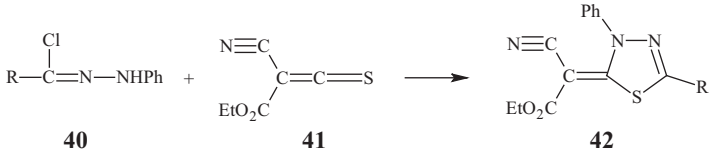
50(a-d)

R= (a) H; (b) $CH_3SO_2CH_2$; (c) H_2NCH_2; (d) CH_3NHCH_2

All of the analogs **50**(**a**–**d**) were tested *in vitro* against a panel of gram-positive and fastidious gram-negative bacteria. Selected compounds were also evaluated for *in vivo* effect against *S. aureus* in a mouse bacteremia model. All of these analogs exhibited good to excellent antibacterial activity, including good activity against fastidious gram-negative organisms. In many cases, the compounds had superior activity to linezolid. The *in vitro* activity of the 1,3,4-thiadiazolyl phenyl oxazolidinones is relatively insensitive to the nature of the substituent at the 2-position. As expected, the thioacetamide analogs **50**(**a**–**d**) are extremely potent against both gram-positive and fastidious gram-negative organisms. Various 1,3,4-thiadiazole analogs had *in vivo* activity comparable to linezolid, but the thioamides lacked oral activity presumably due to metabolism of the thioamide.

Oxazolidinone analogs that contain a 1,3,4-thiadiazole C-ring represent a new class of oxazolidinone antibacterial agents having excellent activity against both gram-positive and fastidious gram-negative organisms.

1,3,4-Thiadiazolyl phenyl oxazolidinones are useful extensions of the quantitative structure-activity relationship of the oxazolidinone class of antibacterial agents (Thomasco et al., 2003).

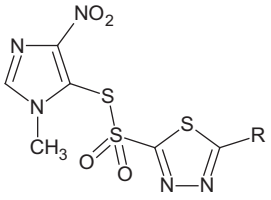


40 **41** **42**

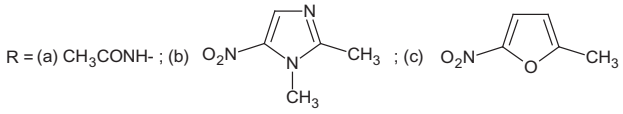
Scheme 7 Synthesis of mercapto-thiadiazoles by 1,3-dipolar cycloaddition reaction.

2.4.3. Sulfonyl-1,3,4-thiadiazoles derivatives

Bahram *et al*. reported the synthesis and antibacterial activity of a new series of 2-(1-methyl-4-nitro-1*H*-imidazol-5-ylsulfonyl)-1,3,4-thiadiazoles **51(a–c)** (Bahram et al., 2011). The three compounds were tested *in vitro* by the conventional agar dilution method against a panel of microorganisms including gram-negative and gram-positive bacteria.



51(a-c)



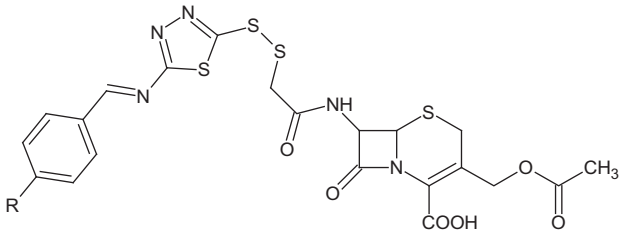
Compound **51c** with 5-(5-nitrofuran-2-yl)-residue on 1,3,4-thiadiazole scaffold had shown promising antibacterial activities against gram-positive bacteria including *S. aureus, Staphylococcus epidermidis* and *B. subtilis* (Bahram et al., 2011).

2.4.4. Newly synthesized cephalosporins

New arylideneamino-(1,3,4-thiadiazol-5-yl)-dithioacetamido-cephalosporanic acids **52(a–d)** have been synthesized and tested *in vitro* antimicrobial activities of the prepared cephalosporins were investigated using a panel of selected microorganisms.

The antimicrobial activities of the newly synthesized cephalosporins as in compounds **52(a–d)** were determined by the agar diffusion method using representative Gram (+) and Gram (−) bacteria on tryptic soya agar media.

The test microorganisms used to evaluate the potential antimicrobial activity of the newly synthesized cephalosporins were: *S. aureus*, *E. coli*, *P. aeruginosa* and *M. luteus*. Cephalexin was used as a reference.



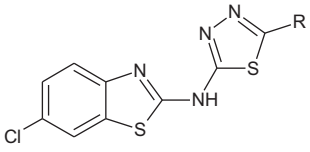
52(a-d)

R = (a) H ; (b) Cl ; (c) Br ; (d) NO_2

Cephalosporins containing 1,3,4-thiadiazole moiety linked through a disulfide bond in the acyl side chain compounds **52(a–d)** were the most potent and were found to be equipotent to cephalexin, especially compounds **52c** and **52d**. This finding was expected and was supported when compared with antibiotics containing disulfide bonds which showed marked activities (Alwan, 2012).

2.4.5. From 6-methyl-1,3-benzothiazol-2-amine

A series of 2-aryl-5-(6′-chloro-1′,3′-benzothoazole-2-yl-amino)-1,3,4-thiadiazoles **53(a–j)** have been synthesized from 6-methyl-1,3-benzothiazol-2-amine and screened for both antibacterial activities using ofloxacin as a standard drug. The compounds were screened against *S. aureus, E. coli* and *P. aeruginosa* in nutrient agar medium.



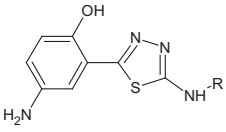
53(a-j)

R = (a) phenyl ; (b) 4-chlorophenyl ; (c) 2,4-dichlorophenyl ; (d) 4-nitrophenyl ; (e) 2-aminophenyl ; (f) 2,4-dichlorophenoxymethyl ; (g) 2-naphthylmethyl ; (h) 4-methoxyphenyl ; (i) 2-acetoxyphenyl ; (j) 3-pyridyl

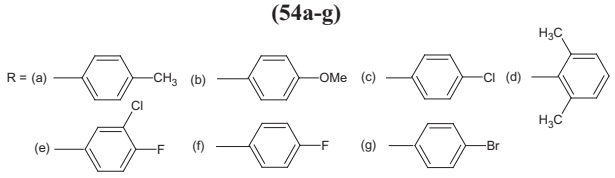
The thiadiazole derivative **53i** having an acetoxy-phenyl group showed potent activity against *S. aureus*, whereas compound **53g** having the 2-napthyl-methyl group showed maximum inhibition against *E. coli*, when compared with standard drug ofloxacin. Compound **53c** having the 2,4-dichloro-phenyl group also showed significant antibacterial activity against *S. aureus, E. coli* and *P. aeruginosa*. Rest of the compounds showed moderate to good antibacterial activity (Amir et al., 2009).

2.4.6. Derivatives of 5-amino-2-hydroxybenzoic acid

Variously substituted 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4-thiadiazole-2-yl} phenol **54(a–g)** were synthesized and evaluated for their antibacterial activity.



(54a-g)



These compounds showed significant antibacterial activity against *S. aureus* and *E. coli* bacteria using the cup plate technique (Hussain et al., 2008).

2.4.7. Conclusions

1,3,4-Thiadiazole and its derivatives proved to be effective against different microorganisms as summarized in Table 2.

3. 1,2,4-Triazole and its derivatives

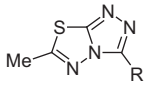
3.1. Introduction

Triazoles are two basic aromatic heterocycle isomers, 1,2,3-triazole (**55**) and its isomer 1,2,4-triazole (**56**).

55

56

1,2,4-Triazole derivatives find uses in a wide variety of applications mostly antifungals such as fluconazole and intraconazole. 4-Amino-5-mercapto-3-substituted-1,2,4-triazole showed antifungal, anti-inflammatory and antitubercular properties that have made them important chemotherapeutic agents (Kurtzer et al., 1965). Some 3,6-disubstituted-1,2,4-triazol[3,4-b]-1,2,4-thiadiazole derivatives (**57**) showed anti HIV-1 activity at concentrations slightly below cytotoxic levels.



57

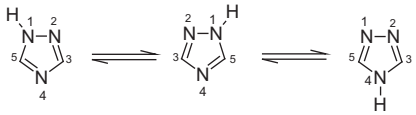
Partially or fully reduced triazoles (thiazolines and thiazolidine respectively) with monovalent substituents are respectively unstable and of little interest. Triazolines and thiazolidines with exocyclic bonds such as ═O, ═S, ═NR′R″, ═CR′R″, etc. are also aromatic (Polya, 1984).

Substituents to aromatic and non-aromatic 1,2,4-triazoles can be situated in all positions of the molecule due to multiple valency of carbon and nitrogen atoms.

Bridgehead nitrogen-heterocyclic compounds obtained by fusion of the 4,5-dihydroimidazole and [1,2,4]triazole nuclei, have identified one compound containing the methylthio group at position 3 and with a 4-methylphenyl substituent at position 7 (e.g., 7-(4-methylphenyl)-3-methylthio-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazole) with a significant antibacterial activity. This heterocycle was strongly active against *S. aureus* and showed superior antibacterial activity to ampicillin (Sztanke et al., 2006).

1,2,4-Triazole and its amino derivatives, tetrazole, thiadiazole, pyrazole, imidazole and the corresponding derivatives have been studied as corrosion inhibitors of copper based material such as bronzes (Khiati et al., 2011).

1,2,4-Triazole (**56**) may exist in equilibrium between three forms: 1H-form(i), 1H-form(ii) and 4H-form as following,



1H-form(i) 1H-form(ii) 4H-form

The calculated energy differences between azole tautomers support preference for the 1*H*over 4*H* tautomer. Similarly, the usual tautomeric preference for triazolines over hydroxytriazoles and aminotriazoles over triazolinimines is supported on thermochemical evidence (Dewar and Morita, 1969).

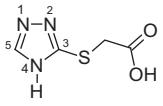
The molecular structure of 1,2,4-triazole (**56**) was determined by gas phase electron diffraction. The internuclear distances and bond angles were obtained by applying a least-squares analysis to the experimental intensity. The bond distances (r_g) and bond angles suggested that the 1,2,4-triazole exists in an 1*H*-form. The bond distances N1–N2 = 1.377 ± 0.010 Å, N2–C3 = 1.329 ± 0.009 Å, C3–N4 = 1.348 ± 0.009 Å, N1–C5 = 1.377 ± 0.004 Å, N4 = C5 = 1.305 Å (calculated value), N1–H = 0.990 Å, C3–H and C5–H = 1.054 Å. The bond angles ∠N1N2C3 = 102.7 ± 0.5°, ∠N2C3N4 = 113.8 ± 01.3°, ∠N2N1C5 = 108.9 ± 0.8°, ∠H1N1N2 = 110.9°, ∠H2C3N4 = 119.2°, ∠H3C5N1 = 121.0°, ∠C3N4C5 = 105.7° (calculated value), and ∠N4C5N1 = 108.7° (calculated value).

Table 2 Effect of investigated compounds of types of bacteria.

Compounds	Gram positive bacteria	Gram negative bacteria
47	+	+
48	+	+
49	+	+
50	+	+
51	+	–
52	+	+
53	+	+
54	+	+

+ Positive effect.
– Negative effect.

Whereas the substituted C3-S-preferred the 4*H*-form based on the crystal structure of 4H-1,2,4-triazole-3-mercapto acetic acid (**58**) which showed that atoms C3,C5,N1,N2,N4 are coplanar and form a conjugated plane with a mean deviation of 0.002 Å.



58

The bond lengths of C3-N2, C3-N4, C5-N4, C5-N1 and N1-N2 are 1.317(2) Å, 1.364(2) Å, 1.328(2) Å, 1.317(2) Å, and 1.362 Å respectively, being in accordance with 4*H*-form (Chiang and Lu, 1977).

3.2. Synthesis of 1,2,4-triazoles and their derivatives

During the last few decades, considerable attention has been paid to synthesize 1,2,4-triazole derivatives possessing comprehensive bioactivities as antibacterial and antimycobacterial (Klimesová et al., 2004).

Several methods for the synthesis of 1,2,4-triazole and its derivatives were reported (Zaharia et al., 2001). One of these methods follows cyclization of aminoacylhydrazines (**60**) and acyl halides as shown in Scheme 8. Sometimes this method may be used into formation of some 1,3,4-oxadiazole derivatives (**61**,**62**) (Gehlen and Blankenstein, 1960).

The most common procedure to synthesize the 1,2,4-triazole-5-thiol derivatives (**64**) is also involving a base catalyzed cyclization of thiosemicarbazides (**63**) or its thio derivative as shown in Scheme 9 (Wheelis, 2007; Zhang et al., 2002) (see Scheme 10).

3.3. Antibacterial activity

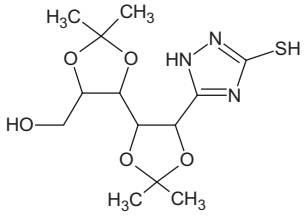
It has been shown that the antiviral and antibacterial activities of thiourea derivatives are due to the presence of the –NH–C(S)–NH– function in the molecule and that changes in this

activity depend on the nature of the substituents (Cansiz et al., 2001). Thus, the substitute groups present in various compounds have different effects against different bacteria.

Regarding antimicrobial activity, triazole is structurally similar to imidazole molecule. Although triazole and imidazole act by the same mechanism of action, triazoles possess advantages over imidazoles, which have slow metabolic rate, oral bioavailability, and less effect on human sterol synthesis. For these reasons imidazoles are slowly being replaced by triazole molecules (Palekar et al., 2009).

3.3.1. From gluconic acid

New acyclo C-nucleosides bearing 1,2,4-triazole-3-thiol (65)moieties derived from gluconic acid were synthesized and tested against *S. aureus, E. faecalis, P. aeruginosa* and *E. coli* using ampicillin as standard.

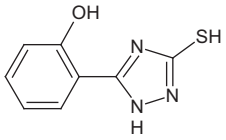


65

The triazole exhibited weaker inhibition effects than ampicillin against these bacteria (Belkadi and Othman, 2011).

3.3.2. From salicylic acid

3-(2-hydroxyphenyl)-1*H*-1,2,4-triazol-5-thiol (**66**) has been synthesized starting from salicylic acid and tested *in vitro* against *E. coli, P. aeruginosa* and *S. aureus* using ampicillin and gentamycin as references.

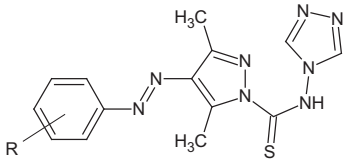


66

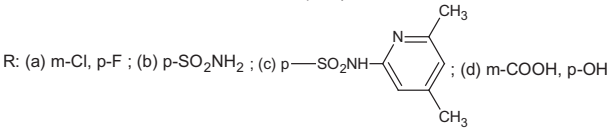
The screening results indicate that the compound 66 showed a moderately active effect against all bacteria tested (Khiati et al., 2007).

3.3.3. From substituted aniline

Hussain et al. synthesized a series of 1-[(1,2,4-triazole-4-yl) carbothioamide]-3,5-dimethyl-4-[(substituted phenyl) diazenyl] pyrazoles **67(a–d)**. These compounds were investigated for their antibacterial activities.

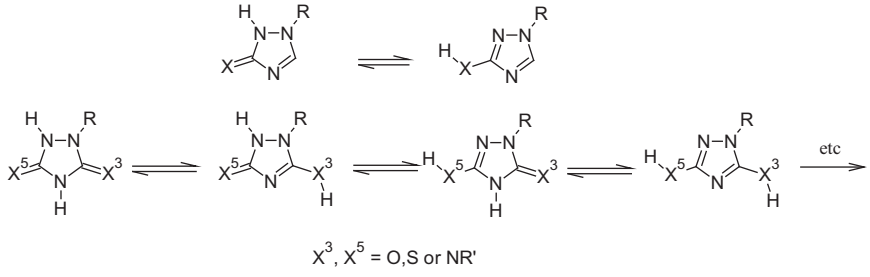


67(a-d)

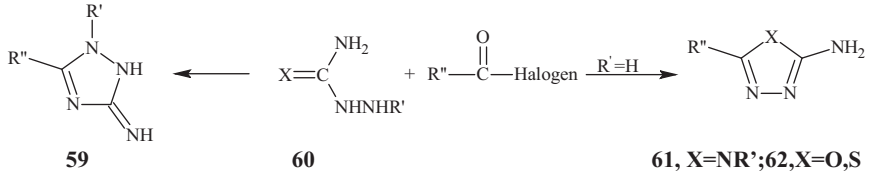


Antibacterial activities of the synthesized compounds were determined *in vitro* against *S. aureus* and *E. coli*. Standard antibiotic ofloxacin was used as reference drug.

These compounds showed moderate antimicrobial activity against tested bacterial strains (Hussain et al., 2010).

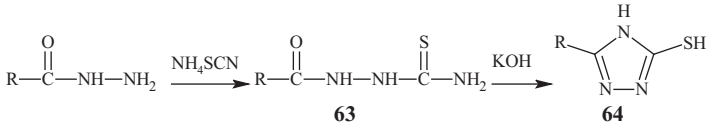


Scheme 8 Tautomeric structures of substituted 1,2,4-triazole.



59 **60** **61, X=NR';62,X=O,S**

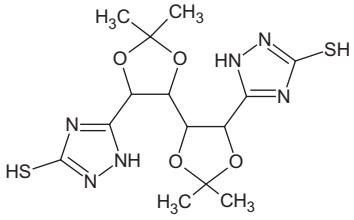
Scheme 9 Synthesis of 1,2,4-triazole.



Scheme 10 Synthesis of 1,2,4-triazole-5-thiole.

3.3.4. From glucaric acid

This bis(1,2,4-triazole-3-thiol) (**68**) derivative of glucaric acid was essayed for antibacterial activity against *P. aeruginosa* and *E. coli* using ampicillin as reference drug.

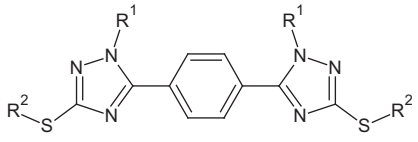


68

The triazole exhibited an important antibacterial activity against these bacteria (Belkadi and Othman, 2011).

3.3.5. From terephthalic acid

5,5′-Benzene-1,4-diylbis(1*H*-1,2,4-triazole-3-thiol) (**69a**) and its derivatives 69(b-c) were synthesized from terephthalic acid and tested *in vitro* against *P. aeruginosa* and *E. coli* and compared with known antibiotics cephalosporin and gentamycin.



69(a-c)

(a) : $R^1 = R^2 = H$; (b) : $R^1 = H$, $R^2 = CH_3$; (c) : $R_1 = R_2 = CH_3$

Triazole **69a** exhibited an intermediate effect on *P. aeruginosa* while methyl triazole **69b** showed a similar effect on the same bacteria. The highest effect was observed by dimethyl triazole **69c** upon *E. coli* at the lowest concentration (Datoussaid et al., 2012).

3.3.6. Conclusions

1,2,4-Triazole and its derivatives proved to be effective against different microorganisms as summarized in Table 3.

4. C–R and N–R derivatives of 1,2,4-triazol-5-thiol

4.1. Introduction

Three categories of derivatives may be observed for 1,2,4-triazoles. The first category is the C–R derivatives, they existed in two types, either C3–R or C5–R and C3–R and C5–R derivatives. The second category involves Cx–R and Ny–R derivatives. The third category involves N1–R derivatives, N2–R derivatives and N1 and N2 derivatives. The C3–R or C5–R and C3–R and C5-R derivatives may be chosen from the beginning of the synthesis by selecting the appropriate starting material such as the wanted carboxylic acid.

4.2. Synthesis

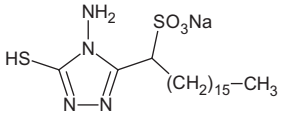
The Nx–R derivatives were either made up by substitution on N– atom or by selecting the appropriate hydrazine derivatives. The **71**, **N4–R** and **72**, **N4–NH$_2$** can be derived from reaction of 1,3,4-oxadiazoles (**70**) with R_3NH_2 or NH_2NH_2 respectively (Palekar et al., 2009) (see Scheme 11).

Another method for preparation of N–NH_2 derivative is by treating the triazoles with methyl iodide.

4.3. Antibacterial activity

4.3.1. From sodium salt of α-sulphonated fatty acid hydrazide

Sodium 1-[4-amino-5-mercapto-4*H*-(1,2,4)triazol-3-yl]heptadecane-1-sulfonate (**73**) has been synthesized.

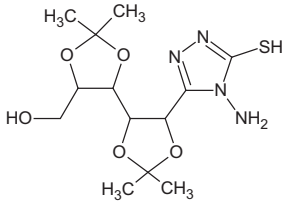


73

The antibacterial activity of the compound was determined *in vitro* against various pathogenic bacteria such as gram positive bacteria (*B. subtilis, S. aureus*) and gram negative bacteria (*E. coli*). The results indicated that the compound was highly active against selected pathogens (El-Sayed, 2006).

4.3.2. From gluconic acid

An acyclo C-nucleoside bearing 4-amino-1,2,4-triazole-3-thiol moieties (74) derived from gluconic acid was synthesized and tested against *S. aureus, a*nd *E. coli* using ampicillin as standard.



74

The activity of the compound is equal to that of ampicillin in terms of antibacterial activity against *S. aureus*. The compound **74** has a moderately active effect on *E. coli* bacteria (Belkadi and Othman, 2011).

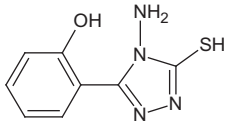
Table 3 Effect of investigated compounds of types of bacteria.

Compounds	Gram positive bacteria	Gram negative bacteria
65	+/−	+/−
66	+/−	+/−
67	+/−	+/−
68	/	+
69	/	+

+ Positive effect.
+/− Moderate effect.

4.3.3. From salicylic acid

3-(2-Hydroxyphenyl)-4-amino-1,2,4-triazol-5-thiol (**75**) has been synthesized starting from salicylic acid and tested *in vitro* against *E. coli* and *S. aureus* using ampicillin and gentamycin as references.

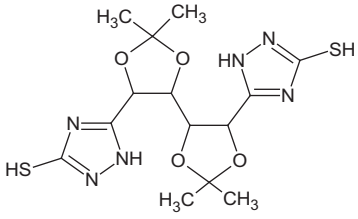


75

The screening results indicate that the compound showed a moderate to slight activity against bacteria tested (Khiati et al., 2007).

4.3.4. From glucaric acid

The bis (4-amino-1,2,4-triazole-3-thiol) (**76**) derivative of glucaric acid was essayed for antibacterial activity against *P. aeruginosa* and *E. coli* using ampicillin as reference drug.

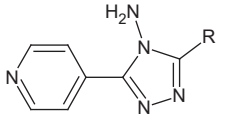


76

The bis-amino-triazole **76** exhibited an important antibacterial activity against these bacteria (Belkadi and Othman, 2011).

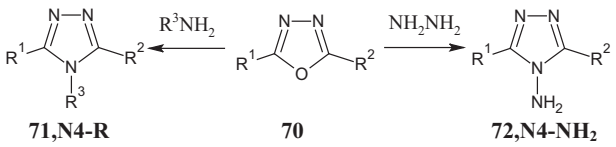
4.3.5. From isoniazid

Synthesized 5-substituted-3-pyridine-1,2,4-triazole **77(a–g)** has been tested for antibacterial activity.



77(a-g)

R = (a) C_6H_5-; (b) 4-C_2H_4-C_6H_4-; (c) 4-NH_2-C_6H_4-; (d) 2-OH-C_6H_4-; (e) 2-NH_2-C_6H_4-; (f) 4-OH-C_6H_4-; (g) 4-CH_3-C_6H_4-



71,N4-R **70** **72,N4-NH_2**

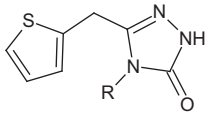
Scheme 11 Synthesis of **71**, **N4–R** and **72**, **N4–NH_2** from oxadiazoles 70.

A cup plate method was employed for the *in vitro* study of antibacterial effect against *B. subtilis*, *S. aureus*, Proteus mirabilis and Salmonella typhi.

The screening result indicates that all compounds exhibited moderate to good antibacterial activities. It was reported that compounds with free NH_2 in the 4th position C **77(a–g)** showed inhibitory effect against one or more types of bacteria and also due to the presence of the triazole ring system in the synthesized compounds, that exhibited antimicrobial activity. Compounds **77(b–d)** showed moderate antibacterial activity. Among the synthesized compounds, compound **77f** showed good antibacterial activity (Muthal et al., 2010).

4.3.6. Triazole containing Thiophene moieties

Some 3-(thenylmethyl)-4-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-one **78(a–e)** derivatives were synthesized by the cyclization reaction of 1-(thiophen-2-ylacetyl)-4-substituted semicarbazide derivatives and were evaluated *in vitro* against several species of aerobic bacteria.



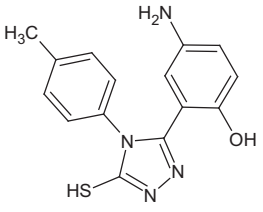
78(a-e)

R = (a) C_6H_5; (b) C_2H_5; (c) 4-$CH_3C_6H_4$; (d) 4-BrC_6H_4; (e) C_6H_{11}

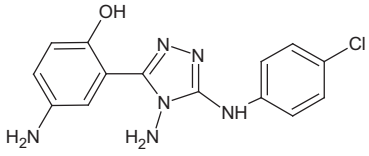
Some of them showed activity against *K. pneumoniae*, *S. aureus, Streptococcus pyogenes* and *P. aeruginosa*. Among tested compounds, the most effective was **78c**. The highest susceptibility to tested derivative was detected in *S. pyogenes*, *P. aeruginosa* and *S. aureus* (Pitucha et al., 2010).

4.3.7. Triazole, amino triazole and thiadiazole derivatives of 5-Amino-2-hydroxybenzoic acid

4-amino-2-[4-(4-methylphenyl)-5-sulfanyl-4H-1,2,4-triazol-3-yl]phenol (**79**), 4-amino-2-{4-amino-5-[(4-chlorophenyl)amino]-4H-1,2,4-triazol-3-yl}phenol (**80**) and 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4-thiadiazole-2-yl} phenol (**81a–c**) were synthesized and evaluated for their antibacterial activity against bacterial strain *S. aureus* and *E. coli*. Ofloxacin was used as standard drugs.



79



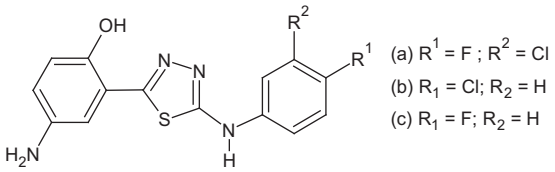
80

Table 4 Effect of investigated compounds of types of bacteria.

Compounds	Gram positive bacteria	Gram negative bacteria
73	+	+
74	+	+/−
75	+/−	+/−
76	/	+
77	+	+
78	+	+
79	+	+
80	+	+
81	+	+

+ Positive effect.
+/− Moderate effect.

Compounds **79** and **80** showed significant antibacterial activity against *S. aureus* (gram-positive) and *E. coli* (gram-negative) bacteria using the cup plate technique.



81(a-c)

The 5-amino-2-hydroxybenzohydrazide derivative (**81a**) having the 3-chloro-4-fluorophenyl amino group at the 2nd position of the thiadiazole ring was found to have MIC 25 μg/mL against *S. aureus* and *E. coli*. 1,3,4-thiadiazole derivatives **81b** and **81c** also exhibited promising antibacterial activity (MIC 25 μg/mL) against *S. aureus* (Hussain et al., 2008).

4.3.8. Conclusions

C–R and N–R derivatives of 1,2,4-triazol-5-thiol proved to be effective against different microorganisms as summarized in Table 4.

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